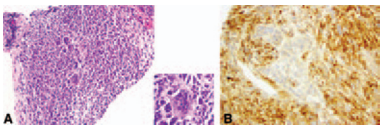
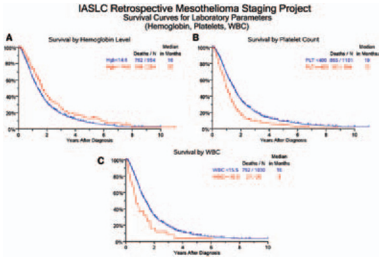
IN THIS ISSUE

- **Small-Cell Lung Cancers in Patients Who Never Smoked Cigarettes**



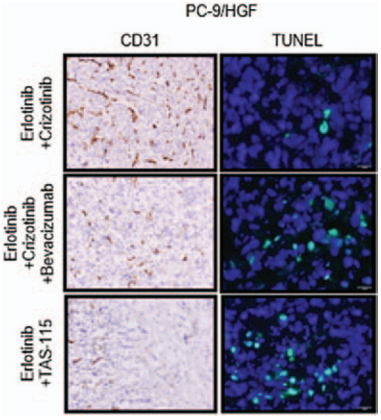
This brief report describes clinical, pathologic, and molecular characteristics of never smokers with small-cell lung cancers (SCLCs). Smoking history, demographic, treatment, and survival data of 1040 SCLC patients (2005–2012) were included in the study. Available samples were analyzed by different molecular tests for *EGFR*, *KRAS*, *PIK3CA*, *ALK,* and RB protein expression. Two percent of SCLC patients were never smokers. Of these, de novo SCLCs accounted for 83% whereas transformation to SCLC was found in 17% in acquired resistance to erlotinib. The median was 23 months from SCLC diagnosis. In de novo SCLC cases, the status of ALK rearrangement (0 of 5), *KRAS* mutations (0 of 8), *EGFR* mutations (2 of 8), and RB loss (6 of 7) were identified. Next generation sequencing of two de novo SCLC cases demonstrated potentially actionable oncogenic drivers—p53 and RB1 mutations with amplification in *TERT* and *CBL* and *GNAS* mutations with amplification in *MYCL1*. (p. 892)

- **Supplementary Prognostic Variables for Pleural Mesothelioma: A Report from the IASLC Staging Committee**



The International Association for the Study of Lung Cancer (IASLC) Staging Committee sought to revise the staging system for malignant pleural mesothelioma (MPM) and have reported supplementary prognostic variables to previously published CORE variables, including stage, histology, sex, age, and type of procedure. Three categories of data were analyzed for supplementary prognostic variables: (1) all data available (pathologic staging and other CORE variables); (2) only clinical staging and Core variables available; and (3) only age, sex, histology, and laboratory parameters. This study determined three prognostic models. Scenario A (all parameters): best pathologic stage, histology, sex, age, type of surgery, adjuvant treatment, WBC (≥ 15.5 or not), and platelets (≥ 400 k or not; $n = 550$). Scenario B (no surgical staging): clinical stage, histology, sex, age, type of surgery, adjuvant treatment, WBC, hemoglobin (<14.6 or not), and platelets ($n = 627$). Scenario C (limited data): histology, sex, age, WBC, hemoglobin, and platelets ($n = 906$). The revision of the prognostic models would allow stratification of patients for optimal outcome after surgery and guide decision to receive adjuvant therapy. (p. 856)

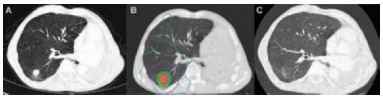
- **Triple Inhibition of EGFR, Met, and VEGF Suppresses Regrowth of HGF-Triggered, Erlotinib-Resistant Lung Cancer Harboring an *EGFR* Mutation**



This study evaluated the effect of triple inhibition of EGFR, Met, and VEGF on HGF-mediated resistance to EGFR TKI in *EGFR*-mutant lung cancer, based on the authors' previous findings of HGF-mediated Met activation in association with EGFR TKI resistance and angiogenesis. *EGFR*-mutant lung cancer cell lines, PC-9, HCC827, and *HGF*-gene transfected PC-9 (PC-9/HGF) cells were used to assess 3 clinically approved inhibitors/antibody, erlotinib (EGFR), crizotinib (ALK and Met), and bevacizumab (VEGF), and a novel TAS-115 (Met and VEGF-2). *In vitro* findings demonstrated crizotinib and TAS-115 blocked Met activation and VEGF production, and reversed resistance to erlotinib triggered by HGF. In vivo findings showed that HGF-mediated angiogenesis was

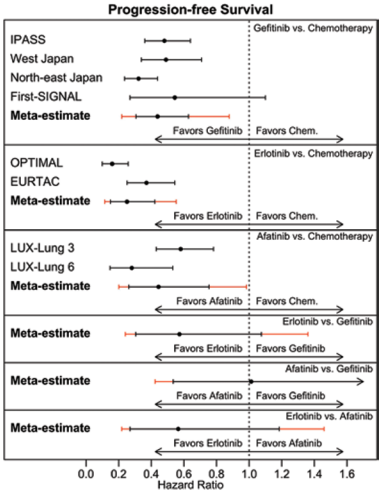
suppressed by bevacizumab and TAS-115. Furthermore, the triplet erlotinib, crizotinib, and bevacizumab, or the doublet erlotinib and TAS-115 resulted in PC-9/HGF tumor growth inhibition and delayed tumor regrowth correlated with continuous block in angiogenesis post-treatment. Taken together, this study suggests that triple inhibition of EGFR, HGF/Met, and VEGF/VEGFR-2 (through clinical drug triplet or TAS-115/erlotinib combination) could reverse resistance to EGFR TKI and inhibit angiogenesis, therefore suppressing progression of *EGFR*-mutant lung cancer. (p. 775)

- **Stereotactic Body Radiotherapy in Patients with Previous Pneumonectomy: Safety and Efficacy**



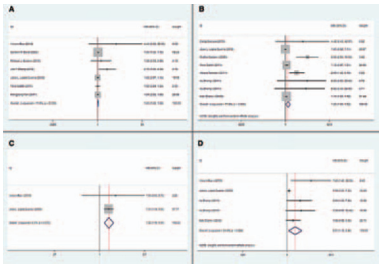
Thompson et al. investigated the safety and efficacy of stereotactic body radiotherapy (SBRT) in patients with prior pneumonectomy. Common Terminology Criteria for Adverse Events version 3.0 was used to report treatment toxicity. Three categories of disease recurrences were defined: local, regional, or distant metastasis. Kaplan-Meier analysis was used to determine overall survival. Thirteen patients with prior pneumonectomy (median age, 69 years), were identified. Fourteen tumors were treated with SBRT in these patients, who were followed up for a median of 24 months. Grade 3 radiation pneumonitis was observed 3 and 4 months post SBRT ($n = 2$), followed by deaths (myocardial infarction in one, progressive dyspnea in another). There were no local recurrences, one regional recurrence and three cases of distant metastatic disease. A median survival of 29 months was achieved; 1-year overall survival (OS) was 69% whereas 2-year OS was 61%. The results indicate that SBRT in patients with prior pneumonectomy could provide local control and long-term survival, but careful planning is necessary in minimizing the risk of radiation pneumonitis. (p. 843)

- **Meta-Analysis of First-Line Therapies in Advanced Non-Small-Cell Lung Cancer Harboring *EGFR* Activating Mutations**



This is the first meta-analysis, which included eight randomized phase 3 clinical trials in the last 5 years, comparing tyrosine kinase inhibitors (TKIs), gefitinib, erlotinib, and afatinib to chemotherapy as first-line therapy in patients with advanced non–small-cell lung cancer (NSCLC) harboring *EGFR* activating mutations. Predictive intervals (PI) were indicative of study-to-study heterogeneity. The findings demonstrated that gefitinib, erlotinib, and afatinib were more superior than chemotherapy in progression-free survival (PFS), overall response rate (ORR), and disease control rate (DCR): hazard ratio meta-estimates for PFS were 0.44, PI 0.22–0.88 (gefitinib); 0.25, PI 0.11–0.55 (erlotinib); and 0.44, PI 0.20–0.98 (afatinib). Similar results were observed for ORR and DCR. No evidence of improved overall survival from gefitinib, erlotinib, or afatinib versus chemotherapy was found. Also, no significant difference between each TKI treatment was observed. This meta-analysis provided evidence to guide first-line treatment decisions for patients with advanced NSCLC bearing *EGFR* activating mutations. (p. 805)

- **Primary Tumor Standardized Uptake Value (SUVmax) Measured on F18-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) is of Prediction Value for Survival and local control in Non-small Cell Lung Cancer (NSCLC) receiving radiotherapy: Meta-Analysis (MA)**



Reliable prognostic factors for predicting radiotherapy (RT) responses are important to select patients for aggressive RT. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT; ^{18}F-FDG PET/CT) has been used in diagnosing, restaging at recurrence, determining RT targets and effects from RT or chemotherapy in patients with NSCLC. This meta-analysis reviewed 13 studies identified from the literature (2005–2013) to evaluate the prognostic values of primary tumor maximum standardized uptake value (SUV_{max}) derived from ^{18}F-FDG PET/CT in NSCLC patients receiving RT. Overall survival (OS) and local control (LC) data were analyzed from these studies with sample sizes ranging from 46 to 132. The results demonstrated that higher pre-RT SUV_{max} was associated with shorter OS (combined HR = 1.05; $P_{heterogeneity}$ = 0.245), and poor LC (combined HR = 1.24; $P_{heterogeneity}$ = 0.0255). Similar results were observed for post-RT SUV_{max}: OS (combined HR = 1.32; $P_{heterogeneity}$ = 0.670) and LC (combined HR = 2.19 and 2.32). When stratified by stereotactic body radiotherapy (SBRT) and conventional radiotherapy (CRT), high pre-SBRT SUV_{max} was significantly associated with poor OS (HR = 1.10; $P_{heterogeneity}$ = 0.245), and unfavorable LC (HR = 1.11; $P_{heterogeneity}$ = 0.242). Post-SBRT SUV_{max} was associated with LC (HR = 2.19; $P_{heterogeneity}$ = 0.204), but OS was not determined because of limited data. In CRT groups, both high pre-CRT and post-CRT SUV_{max} were correlated to poor OS. Taken together, this study demonstrated a significant correlation of high level of pre-RT or post-RT SUV_{max} with higher risk of death and local recurrence, regardless of treatment types (SBRT or conventional radiation). This relationship seemed particularly strong in patients with Stage I NSCLC treated with SBRT. (p. 834)

RESEARCH WATCH

- **Ceritinib in *ALK*-Rearranged Non–Small-Cell Lung Cancer**

Ceritinib (LDK378) is a new ALK inhibitor, which has been shown to be more potent than crizotinib, and exhibited marked antitumor activity in both crizotinib-sensitive and crizotinib-resistant tumors in ALK-positive NSCLC preclinically. In this phase I study, 59 patients with ALK-positive advanced NSCLC received 50–750 mg once daily of ceritinib in the dose-escalation phase whereas 71 patients received the maximum tolerated dose (750 mg/d) in the expansion phase. The overall response rate in patients who received ≥ 400 mg/d of ceritinib was 58%, with a median progression-free survival of 7.0 months. Patients receiving ≥ 400 mg/d of ceritinib showed a response rate of 56% (prior crizotinib) and 62% (without prior crizotinib). Responses were also observed in patients whose disease had progressed on prior crizotinib treatment irrespective of the presence of resistance mutations in *ALK*. The most common toxicities were nausea, diarrhea, vomiting, fatigue, elevated aminotransferase levels. No treatment-related deaths. The authors concluded that ceritinib was highly active in advanced NSCLC with *ALK* rearrangement, including those with disease progression on crizotinib, despite the presence of ALK resistance mutations.

Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-Rearranged Non–Small-Cell Lung Cancer. *New Eng J Med* 2014;370:1189–1197. doi:10.1056/NEJMoa1311107.

- **Transcriptomic Architecture of the Adjacent Airway Field Cancerization in Non–Small Cell Lung Cancer**

This is the first comprehensive study in non–small-cell lung cancer (NSCLC) on the gene expression of the adjacent airway field cancerization, a phenomenon in which large areas of cells are affected by changes leading to cancer. Resected early-stage NSCLC (I-IIIA) samples from 20 patients, normal-appearing adjacent airways and uninvolved lung tissue were analyzed by whole-transcriptome expression profiling. Differentially

expressed gene features ($n = 1661$) were identified between NSCLCs and airways versus normal lung tissues. A statistically significant difference of a subset of these changes ($n = 299$) was observed between airways in lung cancer patients and those in cancer-free smokers ($p < 0.001$). Moreover, significant and progressive differential expression of 422 genes and cancer-associated signaling pathways in airways by distance from tumors was found between NSCLCs and normal lung tissues. Significantly higher level of *LAPTM4B*, which has been found in other solid tumors, were detected in airways closer to tumors ($p < 0.05$), and in cancer cells versus normal bronchial epithelial cells ($p < 0.001$). Overexpression of *LAPTM4B* can induce certain chemotherapy resistance. Further studies were planned in larger populations to evaluate field cancerization in other lung cancer subtypes and in smokers and nonsmokers. The findings on adjacent airway field cancerization could shed lights on NSCLC carcinogenesis and detection.

Kadara H, Fujimoto J, Yoo S-Y, et al. Transcriptomic architecture of the adjacent airway field cancerization in non–small cell lung cancer. *J Natl Cancer Inst* 2014. doi:10.1093/jnci/dju004.

- **Short-Term Cigarette Smoke Exposure Leads to Metabolic Alterations in Lung Alveolar Cells**

Agarwal et al. investigated the effect of cigarette smoke (CS) exposure on the metabolism in alveolar type II cells in vivo. Mice were exposed to either air or CS produced by a smoking machine for 4 or 8 weeks. Alveolar type II cells were collected for analysis. The findings showed that acute CS exposure resulted in alveolar destruction. The XF Extracellular Flux Analyzer revealed the effect of CS exposure on cellular respiration, indicating altered glycolysis and increase in palmitate consumption, as evidenced by increased palmitate transport into the cells and mitochondria. The enhanced palmitate consumption for energy production in turn disrupted the surfactant biosynthesis pathway: phosphatidylcholine levels declined and phospholipase A2 activity increased. To conclude, this study sheds lights on the mechanism of surfactant deficiency in smokers and suggests a potential target to tackle the onset of COPD.

Agarwal AR, Yin F, Cadenas E. Short-term cigarette smoke exposure leads to metabolic alterations in lung alveolar cells. *Am J Respir Cell Mol Biol* 2014. doi:10.1165/rcmb.2013-0523OC.

- **Clove Cigar Sales Following the US Flavored Cigarette Ban**

Delnevo and Hrywna reviewed industry documents and reported the changes in marketing and production strategies of Kretek International (Djarum cloved cigars parent company) after the ban on flavored cigarettes that included clove cigarettes, excluding cigars, by the US Family Smoking Prevention and Tobacco Control Act in 2009. The analysis covered clove cigar sales trends in the United States (2009–2012) after the ban, and tobacco imports from Indonesia to the United States from the USDA (2008–2012). The results demonstrated a dramatic increase in clove cigar sales by greater than 1400% between 2009 and 2012 immediately after the ban. A shift from cigarettes to almost exclusively cigars in the tobacco imports from Indonesia to the United States was also observed in the same period. The authors concluded that Kretek International manipulated the regulatory loopholes after the ban and replaced the banned clove cigarettes with clove cigars, of which consumption was therefore increased dramatically recently.

Delnevo CD, Hrywna M. Clove cigar sales after the US flavored cigarette ban. *Tob Control* 2014. doi:10.1136/tobaccocontrol-2013–051415.

- **A Review of Smoking Policies in Airports Around the World**

This is a review conducted by Stillman et al. to compare smoking policies of 34 major international airports in five world regions with the corresponding national and subnational legislation on smoke-free indoor places. Anecdotal data on smoking regulations and practices in specific airports from an online traveler website were also included in the review. Over 50% of the airports had designated smoking areas. About 56% of the airport locations had national legislation allowing designated smoking areas, whereas 35.3% were smoke free. Sixty percent of the airport locations had subnational legislation restricting smoking, whereas 40% were smoke free. Although 71.4% of the airport locations allowed more stringent smoke-free laws at the subnational level versus the national level, these laws were implemented in only half of these places. Taken together, airports are often being overlooked in national or subnational smoke-free policies. Actions are needed in lowering secondhand smoke exposure among travelers and workers in airports with smoke-free policy enforcement, and informing future airport tobacco control policy with consistent terminology and definitions.

Stillman FA, Soong A, Kleb C, Grant A, Navas-Acien A. A review of smoking policies in airports around the world. *Tob control* 2014. doi:10.1136/tobaccocontrol-2013–051364.

- **FDA E-cigarettes: Impact on Individual and Population Health.**

This is an open access supplement to the journal, *Tobacco Control*, comprising original articles that highlight the current knowledge and research gaps with regards to e-cigarettes in product design, chemistry, and toxicology of the contents of e-liquid and vapor, human risk factors, abuse liability, clinical pharmacology and human health effects, and issues on pediatric and environment.

Tob Control 2014;23(suppl 2):1–58.

NEWS IN BRIEF

- **ELCC 2014: PD-L1 and PD-1 Expression in Molecularly Selected Non-Small-Cell Lung Cancer (NSCLC) Patients**

At the Fourth European Lung Cancer Congress (ELCC), D'Incecco and colleagues presented the findings of their study on the expression of programmed death 1 (PD-1) and its ligand, PD-L1, in 125 NSCLC patients harboring mutated *EGFR* (44.8%), mutated *KRAS* (23.2%), *ALK* translocation (8%), and wild-type *EGFR*/*KRAS*/*ALK* (24%). There was a significant association between PD-L1 expression and *EGFR* mutations ($p < 0.0001$) and between PD-1 expression and *KRAS* mutations ($p = 0.005$). In gefitinib or erlotinib-treated cohorts, PD-L1-positive patients, when compared with PD-L1-negative patients, were correlated with higher response rate (RR: 61.2% versus 34.8%, $p = 0.010$), longer time to progression (TTP, 11.7 versus 5.7 months, $p < 0.0001$) and longer overall survival (OS, 21.9 versus 12.5 months, $p = 0.087$). In the subset of patients with *EGFR* mutation receiving EGFR tyrosine kinase inhibitors (TKIs), PD-L1 expression was associated with longer TTP (13.0 versus 8.5 months, $p = 0.011$) and a trend of better OS (29.5 versus 21.0 months, $p = 0.752$). There was no difference in RR, TTP, and OS between PD-1-positive and PD-1-negative patients. These results warrant further studies of the combination of PD-L1 or PD-1 blockade with EGFR TKIs or other targeted therapies to improve outcome of patients with *EGFR* or *KRAS* mutant NSCLC.

- **ELCC 2014: Programmed Cell Death 1 Ligand 1 (PD-L1) Expression and Association with Survival in Mesothelioma**

Mansfield et al. evaluated the potential of PD-L1 as a therapeutic target by analyzing its expression in 224 cases (1986–2003) of malignant pleural mesothelioma (MPM) and its association with clinical outcome. The findings, presented at the ELCC 2014, demonstrated that PD-L1 was expressed in 40% of the study samples. No difference in gender, age, decade of diagnosis, or lymphocytic infiltration was observed between PD-L1-positive and PD-L1-negative patients. PD-L1-positive patients were less likely to undergo surgery as a result of disease progression ($p = 0.001$) and had poorer survival compared with PD-L1-negative patients (6 versus 14 months; $p < 0.0001$). Its association with poor survival remained significant after adjusting for age, gender, lymphocytic infiltration, and therapeutic surgical intervention (risk ratio 1.73; $p = 0.0002$). Taken together, substantial PD-L1 expression in MPM and its correlation with worse survival could be valuable in MPM patient management.

- **ELCC 2014: Clinical Utility of a Plasma-Based MicroRNA Signature Classifier within Computed Tomography Lung Cancer Screening**

Plasma microRNAs (miRNAs) signatures have been reported previously to have strong predictive, diagnostic, and prognostic values in disease-free smokers from two independent spiral-CT screening trials. Pastorino et al. of the same group presented their findings at ELCC 2014 on a retrospective study of the diagnostic performance of a plasma microRNA signature classifier (MSC) in smokers (69 lung cancer and 870 disease free) enrolled in the randomized Multicentre Italian Lung Detection (MILD) trial. Across both low-dose CT (LDCT, $n = 652$) and observation arms ($n = 287$), MSC for lung cancer detection demonstrated 87% sensitivity and 81% specificity, and 88% and 80% respectively in the LDCT arm. LDCT had sensitivity of 79% and specificity of 81%. In all subjects, the negative predictive value of MSC for detection was 99% and that for death-by-disease was 99.86%. LDCT false-positive rate dropped from 19.4% to 3.7% when combined with MSC. MSC risk groups were significantly correlated with survival ($p < 0.0001$). All in all, the results from this large validation study demonstrated the predictive, diagnostic, and prognostic value of MSC and its potential in enhancing LDCT efficacy in lung cancer screening.

- **AACR 2014: MK-3475 (Anti-PD-1 Monoclonal Antibody) for Non-Small Cell Lung Cancer (NSCLC): Antitumor Activity and Association with Tumor PD-L1 Expression**

At the 105th American Association for Cancer Research (AACR) Annual Meeting, Gandhi et al. presented updated data on the relationship of tumor PD-L1 expression with overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) from the treatment with MK-3475, an anti-PD-1 antibody. The phase I study included 38 previously treated NSCLC patients receiving MK-3475, whose tumor response were analyzed by immune-related response criteria (irRC) and by RECIST v1.1. Immunohistochemistry was used to assess tumor PD-L1 expression. The entire cohort showed an ORR of 24%, median PFS of 9 weeks, and median OS of 51 weeks. Of the 31 patients with evaluable tumor, tumor PD-L1 expression was significantly associated with ORR ($p < 0.001$), PFS ($p = 0.004$), and OS ($p = 0.024$). The authors concluded that there is a significant association between tumor PD-L1 expression and tumor response, PFS and OS in NSCLC patients treated with MK-3475. Together with the preliminary finding of low tumor PD-L1 expression in association with modest antitumor activity, this study suggests the role of PD-L1 as a biomarker for NSCLC patients receiving MK-3475 treatment.

- **AACR 2014: Identification of Somatic Mutations in EGFR/KRAS/ALK-Negative Lung Adenocarcinoma from Never Smokers**

This study aimed to analyze the genetic profile of *EGFR/KRAS/ALK*-negative lung adenocarcinoma ($n = 70$) of never-smoker patients using whole exome sequencing. Kim *et al*. presented their findings at the AACR annual meeting 2014 in San Diego, CA. Among the 27 genes identified, there were genes in the PI3K/mTOR signaling and receptor tyrosine kinase signaling in addition to some genes that were not reported in lung adenocarcinomas previously, such as *SETD2* and *PBRM1* (chromatin remodeling), *CHEK2* and *CDC27* (cell cycle), *CUL3* and *SOD2* (oxidative stress), and *CSMD3* and *TFG* (immune response). This indicates the diversity of the mutations found in *EGFR/KRAS/ALK*-negative lung adenocarcinoma in never smokers. The highly mutated gene was *TP53* (11%); most of the mutations involved genes in cell cycle/DNA repair ($p < 0.001$) and cAMP-mediated protein kinase A signaling ($p < 0.001$). This result indicated that cell cycle/DNA repair was potentially disrupted in lung tumorigenesis and could be candidate therapeutic targets.

- **AACR 2014: Telomere Length in White Blood Cell DNA and Lung Cancer: A Pooled Analysis of Three Prospective Cohorts**

To determine the association of telomere length with risk of lung cancer, Seow et al. pooled their analysis of prospective cohorts from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial in the United States, with the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) trial in ever smoking males in Finland, and the Shanghai Women's Health Study (SWHS) in primarily never smoking women. Analysis of the three studies included blood samples collected before lung cancer diagnosis and measurement of telomere lengths using monochrome multiplex quantitative PCR in a total of matched 847 cases and 847 controls. Consistent with findings from the ATBC and SWHS studies, the PLCO trial demonstrated that longer telomere length was significantly associated with lung cancer risk (adjusted odds ratio, OR: 1.00; p-trend = 0.011). The pooled analysis had an adjusted OR of 1.00 and p-trend of 0.000022. Patients with adenocarcinoma were diagnosed more than 6 years after blood collection showed a more pronounced association. The authors concluded that increased telomere length in white blood cell DNA could be a biomarker of increased lung cancer risk in diverse populations.

- **AACR 2014: Differences in Nicotine Metabolism Among Five Racial/Ethnic Groups with Disparate Risks for Lung Cancer: The Multiethnic Cohort Study**

Park et al. aimed to dissect the underlying mechanism of the different lung cancer risk across racial ethnic groups by investigating nicotine metabolism, which in turn affects smoking behavior, in 2300 smokers without cancer from five racial/ethnic groups: African Americans (AA), Native Hawaiians (NH), Japanese Americans (JA), and Latinos (LA). Total and free urinary nicotine metabolites (nicotine, cotinine, and trans-3-hydroxycotinine [3-OH]) were measured. Urinary nicotine equivalents (NE; sum of total cotinine, total nicotine and total 3-OH) were quantified for smoking dose. Glucuronidation of each nicotine metabolite and *CYP2A6* enzymatic activity were also analyzed. Significant difference was found in NE, glucuronidation of nicotine metabolites, and CYP2A6 activity between race/ethnicity ($p \leq 0.002$). Highest levels of NE and CYP2A6 activity were observed in AA. Also, higher NE was significantly associated with higher CYP2A6 activity for all racial/ethnic groups except NH (p interaction < 0.005). The study demonstrated that the influence of CYP2A6 activity on smoking dose was beyond cigarettes per day and warrants further studies on nicotine biomarkers and racial differences in lung cancer risk.

- **UK Lung Cancer Rates Raised by Three Quarters in Women While Halving in Men**

A new Cancer Research UK report revealed an increase of 73% in lung cancer incidence in women over the last four decades (23.5 per 100,000 in 1975 to 40.6 in 2011). In contrary, incidence in men has declined by 47% over the same period (111.8 per 100,000 to 59.0). A 20% drop in lung cancer incidence was observed in overall UK population. The findings call for renewed efforts to tackle the disease and changing attitudes toward lung cancer. Cancer Research UK emphasized key priorities, such as improving awareness of lung cancer signs and symptoms, continue to reduce smoking incidence through implementation of plain packaging for tobacco products, support for smokers to quit smoking, and addressing the attitude that lung cancer diagnosis is a death sentence.

- **Trade Agreements, ISDS and Plain Packaging**

The introduction of plain packaging for cigarettes is seen as a major advance in tobacco control. Plain packing legislation was introduced in Australia in 2012, coming into full effect in December 2012. The April issue of The Saturday Paper, an Australian weekly (www.thesaturdaypaper.com.au) reports on the legal process underway to oppose this, taking place between Australia's trade lawyers and the tobacco company Philip Morris, International (PMI). The paper reports this as an abuse of international trade agreements. The core of the attempt by PMI is based on Investor-State Dispute Settlement (ISDS) provisions contained within trade agreements to protect companies from poor decisions by governments in countries with weak or biased legal systems. These provisions allow corporations to take legal actions, such as that taken by PMI against Australia; such provisions have been used by other industries, including mining and the pharmaceutical industries. It is a complex arena, involving other countries brought into conflict with Australia with complaints about tobacco laws. These countries include Ukraine, Honduras (British American Tobacco has admitted providing direct assistance to these two), Indonesia, the Dominican Republic, and Cuba. ISDS provisions, reports the paper, are now under reconsideration; various countries, including Australia, have negotiated or are negotiating free trade agreements without ISDS provisions. The intricacies of all of this are also highlighted by a paper from the Center for Policy Analysis on Trade and Health (http://www.cpath.org/sitebuildercontent/sitebuilderfiles/CPATH_PITAC.pdf). Their website (www.cpath.org) includes links to information on the Trans Pacific Partnership Agreement (TPPA) a major trade agreement subject to "tobacco giant subterfuge" (ed.). Much of this is unfamiliar territory to the non-industrial relations community, but for those of us in the scientific and clinical communities buoyed by the successful introduction of plain packaging, these complex multilayered attacks call for our attention, understanding, and opposition.

The full article from The Saturday Paper is available at http://www.thesaturdaypaper.com.au/opinion/topic/2014/03/08/big-tobaccos-plan-stub-out-plain-packaging/1394197200#.UyL8NIWeZl

- **Tobacco Farms, Smoking Rates, the Attorneys-General, and the Pharmacies**

The Washington Post, on March 14, 2014, reported on the prevalence of smoking in various states across the United States (http://www.washingtonpost.com/blogs/govbeat/wp/2014/03/14/the-united-states-of-smoking-the-state-with-the-most-tobacco-farms-smokes-most-often/). Factors that may relate to smoking prevalence include the high number of tobacco farms in the state—Kentucky with 30% smoking prevalence; Mormon population—Utah, where 5% of Mormons smoke, below the national average and perhaps most amenable to intervention, strict smoking bans (workplace, restaurants, and bars) present in the 10 states with the lowest smoking rates in the United States (Utah, California, Minnesota, Massachusetts, New Jersey, Maryland, Washington, Rhode Island, Colorado, Arizona).

The decision of the American drugstore CVS to stop selling tobacco products by October 2014 has received wide acclaim and coverage by many news outlets including National Public Radio (http://www.npr.org/

blogs/thetwo-way/2014/02/05/271906167/cvs-to-stop-selling-tobacco-products) and the Wall Street Journal, Reuter, and CNN. This decision has now been followed by calls from state Attorneys-General to five other major retailers to do the same, including Walgreens, Rite Aid, Wal-Mart, Safeway, and Kroger. A brief report from NPR covers the CVS decision, reporting a possible $2 billion loss in annual revenue from the company's 7600 pharmacies (second behind Walgreens with 8200 pharmacies).